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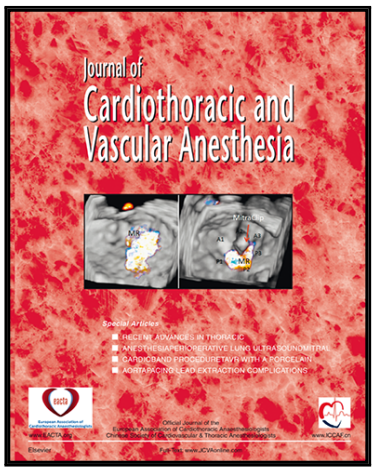

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Bleeding complications in patients with perioperative COVID-19 infection undergoing cardiac surgery: a single-center matched case-control study

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ABSTRACT

Objective: Previous studies reported a poor outcome in COVID-19 patients undergoing cardiac surgery. Complications most frequently described were respiratory failure, renal failure and thromboembolic events. In our recent experience we observed a very high incidence of bleeding complications. The purpose of the study was to investigate a possible significant correlation between perioperative COVID-19 infection and hemorrhagic complications compared to non-Covid patients.

Design: Single-center, observational, retrospective, matched case-control (1:2) study involving patients who underwent open heart cardiac surgery from February 2020 to March 2021 with positive perioperative diagnosis of COVID-19 infection, matched with patients without COVID-19 infection.

Setting: Cardiac Surgery Unit and Intensive Care Unit of an university tertiary center in a metropolitan area.

Participants: In the study period 773 patients underwent cardiac surgery on cardiopulmonary bypass (CPB). Among them 23 consecutive patients had perioperative diagnosis of COVID-19 infection (study-group). These patients were compared with 46 corresponding controls (control-group) who matched for age, sex, BMI and STS score.

Interventions: Open-heart cardiac surgery on cardiopulmonary bypass (CPB).

Measurements and Main results: In the study-group 2 patients (9%) died in the Intensive Care Unit from severe respiratory failure, shock and multiple organ failure. In the study group patients showed a significantly higher incidence of bleeding complications (48% vs 2%, p=0.0001) and cases of surgical reexploration for bleeding (35% vs 2%, p=0.0001), a higher incidence of severe postoperative thrombocytopenia (39% vs 6%, p=0.0007), and a higher need of blood components transfusions (74% vs 30%, p=0.0006). Chest tubes blood loss and surgical hemostasis time (SHT) were markedly prolonged (p=0.02 and p=0.003 respectively).

Conclusions: A worrisome increased risk of early and late bleeding complications in COVID-19 patients was observed, and it should be considered when assessing the operative risk. CPB-related inflammatory reaction could exacerbate the deleterious effect of COVID-19 on the coagulation system and likely deviate it towards a hemorrhagic pattern.

Highlights

- Coronavirus infection is confirmed to markedly increase the postoperative risk.

- A higher rate of hemorrhagic complications and surgical reexplorations for bleeding was observed.
- Coronavirus infection should be taken in account as a risk factor for postoperative bleeding.

Keywords: COVID-19; Intensive Care Unit; cardiac surgery; bleeding.

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) infection pandemic has markedly affected surgical activity and, in particular, cardiac surgery, worldwide.[1-7] In many centers, the number of elective surgical cases decreased and patients undergoing surgery that could no longer be delayed, experienced worse outcomes with increased mortality rate and postoperative complications incidence.[1,5,7-9] Among coronavirus disease 19 (COVID-19) patients, the most frequent complications included interstitial pneumonia with respiratory failure and acute respiratory distress syndrome (ARDS), acute renal failure and thromboembolic events.[1,6-15] However, during surgery in COVID-19 patients, perioperative bleeding was less observed, and has not been thoroughly investigated. Moreover data regarding postoperative bleeding are limited.

Main endpoint of the present study was to evaluate whether patients with perioperative COVID-19 who underwent cardiac surgery with cardiopulmonary bypass (CPB) present an increased risk of hemorrhagic complications. More specifically, we considered as “hemorrhagic complications” the rate of surgical reexploration for bleeding (via mediastinal revision through full resternotomy or subxiphoid pericardial drainage); intracranial hemorrhage, and massive ~~hematic~~ hemorrhagic pleural effusion requiring drainage.

The mortality rate, the incidence of severe thrombocytopenia, need for blood component~~s~~ transfusions and procoagulant drugs, length of surgical hemostasis time (SHT), blood loss

from drains, and length of hospitalization were also analyzed.[12-15] The aim of this study was to evaluate whether possible inflammatory reactions associated with perioperative COVID-19 infection could contribute to coagulation derangements of CPB and consequently, significantly increase the risk for hemorrhagic complications.

Methods

The present study was a retrospective, matched (1:2) case-control analysis. Data were acquired from an electronic database of patients undergoing elective, urgent, or emergency cardiac surgery requiring CPB. Patients were operated on in our Cardiac Surgery Unit from February 2020 to March 2021.

The study was approved by the Ethics Committee of our University Polyclinic (Approval number: 0051824/20; Protocol ID 3663).

Given the retrospective nature of the study and the use of anonymized patient data, requirements for *ad-hoc* patient consent was waived.

Due to the severity of the COVID-19 pandemic, in our region, surgical activity was markedly reduced in most hospitals, and patients with a need for cardiac surgery were compelled to concentrate in a few metropolitan centers, including our Polyclinic.

Regardless, in our center an overall reduction of 87 cardiac surgery cases from 2019 to 2020 was recorded.

As a regional reference center for COVID-19 care, in the study period, this hospital admitted more than 4800 COVID-19 patients (more than 450 of these patients were hospitalized in the Intensive Care Unit). Except for patients with type A aortic dissection, the surgical indication of COVID-19 patients was, in all instances, validated by the internal Institutional Heart Team and was deemed urgent and to delayable (due to unstable angina or chest pain, heart failure, endocarditis, large aneurysm or rapid aneurysmal growth).

Diagnosis of SARS-CoV-2 infection was confirmed via positive throat swab test and Real-Time Polymerase Chain Reaction assay (RT-PCR), which were routinely performed at pre-hospitalization, on admission and daily during the postoperative course.

On admission, data regarding patient's medical history were carefully collected. Chest X-ray and chest computed tomography scan were performed when indicated. Personal protective equipment was provided to medical and paramedical health workers, and care staff was limited to essential professionals. Orotracheal intubation was mostly performed using a video laryngoscope. The postoperative intensive care unit and hospital ward for COVID-19 patients were isolated from other hospital areas. According to the land Health Authority directives, direct contact between patients and their family members was not permitted, and information regarding the patient's clinical condition was conveyed via telephone.

Operations were performed by eight surgeons with an experience of conducting at least 200 procedures each. Patients were operated on through median sternotomy and central cannulation for CPB. For CBP priming the extracorporeal circuit was filled with about 1500 milliliters of Ringer Lactate and about 80-100 milliliters of mannitol.

In the postoperative period patients were mechanically ventilated using a volume controlled ventilator and extubated, usually 6-8 hours after surgery, in the absence of complications, after having reached satisfactory levels for blood gases in spontaneous breathing and adequate lung ventilation, as documented by chest X-ray.

During the postoperative course, red cell transfusion was administered when hemoglobin levels reached 6-7 g/dL and hematocrit was at 22-24%. Platelets were transfused in patients with bleeding manifestations when the platelet count (PLTs) decreased to 80-100.000/ μL. To improve hemostasis and increase filling pressure, fresh frozen plasma (FFP) was administered, when deemed necessary. Mediastinal reexploration for bleeding was considered indicated in cases wherein the rate of blood loss was > 300-400 mL for

one hour or > 200-300 mL during the subsequent hours. Hemodynamic instability and hypotension refractory to medical therapy reinforced the indication for mediastinal revision.

In addition to the primary and secondary endpoints previously described, attempts were made to indirectly quantify the time taken by surgical maneuvers to achieve hemostasis (SHT, Surgical Hemostasis Time). For this purpose, the time interval (in minutes) from the end of CBP (protamine administration) and the beginning of ~~sternal synthesis~~ sternal closure was retrospectively evaluated, which are time intervals routinely recorded by the anesthesiologist.

Patient group matching was based on age (within ± 3 years), sex, body mass index (BMI, within 2 points) and STS (Society of Thoracic Surgeons) score (within 2 points). When multiple control candidates met the core matching criteria, the choice was based on the date of cardiac surgery. The investigators were blinded to case outcomes during matching.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Data with non-normal distribution were assessed using the Mann-Whitney U test, and expressed as median and selected centile (25^{th}-75^{th}). Data with ~~a~~ normal distribution were assessed using the Student's t test. Categorical variables were expressed as proportions, and compared using the chi-squared test or Fisher's exact test, as appropriate. Differences with p=< 0.05 were considered to be statistically significant. The crude odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated for each clinically relevant variable. Variables that reached p= <0.1 in the univariate analysis were included in the multivariable logistic regression analysis. A stepwise selection procedure was used to select variables for inclusion in the final model. The Hosmer–Lemeshow goodness-of-fit test and receiver operating characteristic (ROC) curve analysis were used to assess the goodness of the logistic final model.

All statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, WA, USA).

Results

A total of 826 consecutive patients underwent cardiac surgery at our Polyclinic, from February 2020 to March 2021, of whom 773 required CPB. Among these, 23 patients, age 68.7 ± 8.3 years, 19 (83%) male, had a perioperative diagnosis of COVID-19. On admission, 6 (26%) patients were receiving acetylsalicylic acid, 3 (13%) double antiplatelet drugs and 4 (17%) oral anticoagulants.

Of the four COVID-19 patients at the time of surgery, three were receiving acetylsalicylic acid, and one was not receiving any therapy. In the control group, 13 (30%) patients were treated with acetylsalicylic acid (p=0.3).

Among patients undergoing elective procedures, medications were discontinued in a timely manner before surgery, and of those who underwent emergency surgery, only one was being treated with acetylsalicylic acid.

The study-group was composed ~~by~~ of patients with a perioperative diagnosis of COVID-19, confirmed by positive throat swab test results between 30 days before and 7 days after surgery. Four (17%) patients presented with COVID-19 infection (positive swab test result) on admission, 5 (22%) patients had a recent history (within 30 days) of COVID-19 infection with a negative swab test result on admission, and 14 (61%) patients had a COVID-19 infection that was detected early postoperatively (within 7 days of surgery). Only one patient with positive COVID-19 infection at time of surgery underwent an operation for type A aortic dissection repair.

As the time of positive test after the initial infection is variable, the exact beginning of the infection was not identifiable. Therefore we considered COVID-19 patients all positive

ones in the time period from 30 days before surgery up to 7 days after surgery. So doing the Covid inflammatory reaction should have been present in all patients.

Symptomatic patients were identified and considered acute, all other patients were considered Covid positive and were included in the COVID-19 series on the basis of the laboratory swab positivity. Indication for emergent/urgent surgery was mainly related to the cardiac disease requiring immediate or prompt surgery.

Among the four COVID-19 patients, only one patient exhibited typical coronavirus symptoms, such as severe dyspnea, asthenia, and fever along with minor radiological signs of interstitial pneumonia requiring non-invasive ventilation (NIV). On admission, none of the patients necessitated intubation and neither did any patients require perioperative extracorporeal membrane oxygenation (ECMO) support.

~~The surgeries were performed by eight surgeons with an experience of conducting at least 200 procedures each. Patients were operated on through median sternotomy and central cannulation for CPB. For CBP priming, the extracorporeal circuit was filled with about 1500 milliliters of Ringer Lactate and about 80-100 milliliters of mannitol.~~

Cold crystalloid cardioplegia was administered to 14 (69%) patients, and mixed cold hemato-cystalloid cardioplegia to 9 (39%) patients. Four (17%) patients underwent surgery via a mini-sternotomy approach. Patients with type A aortic dissection underwent circulatory arrest with moderate hypothermia (25-28°C) and antegrade cerebral perfusion. As usual in in our center, the pericardium was left open in all patients.

None of the patients exhibited hematological disorders except for one with a congenital XI coagulation factor deficit, and one with a history of non-Hodgkin lymphoma, neither of which tested positive for COVID-19 at the time of surgery. Preoperative laboratory investigations, blood count and coagulation profiles were normal in all patients.

~~In the postoperative period patients were mechanically ventilated using a volume controlled ventilator and extubated, usually 6-8 hours after surgery, in the absence of~~

~~complications, after having reached satisfactory levels for blood gases in spontaneous breathing and adequate lung ventilation, supported by X-ray documentation.~~

COVID-19 group patients were compared with 46 corresponding controls with no history or evidence of COVID-19 (baseline characteristics are summarized in Table 1). There were no significant between–cohort differences in terms of preoperative characteristics (Table 1). In both the groups, three (13%) surgeries were performed on an urgent-emergent basis (type A aortic dissection). STS score for morbidity and mortality was comparable (11 ± 6.9% vs 8.1 ± 5.8, *p*=0.3) . CBP time in the study group was 152 ± 79 minutes (vs 130 ± 45, *p*=0.08), and aortic cross-clamping time was 106 ± 36 minutes (vs 86 ± 27 minutes, *p*=0.07). SHT was significantly prolonged in the study-group (81 ± 56 vs 64 ± 45 minutes, *p*=0.0003). (Table 1)

Postoperative data are summarized in Table 2. In the study-group, severe respiratory failure was observed in 6 (26%) patients, two (9%) of whom died from ARDS, cardiovascular shock and multiple organ failure. Bleeding complications occurred in 11 (48%) patients. In 8 (35%) patients, surgical reexploration for bleeding was required, four of whom underwent reoperation at least once for late (after the postoperative day six) ~~hematic~~ hemorrhagic pericardial effusion and cardiac tamponade (Fig.1). Six patients were reoperated on during their in-hospital postoperative course, and two were urgently rehospitalized for cardiac tamponade two weeks and three months after surgery, respectively. Four (17%) patients underwent multiple mediastinal reexplorations for recurrent bleeding, three of whom required two mediastinal revisions and one required three revisions. In one patient, ~~a~~ temporary mediastinal packing was performed with subsequent sternal ~~synthesis~~ closure. Among them, only one patient had positive COVID-19 diagnosis at the time of the first operation. In summary, 13 surgical reexplorations were performed in 8 patients (eight mediastinal revisions through resternotomy and five through

a subxiphoid approach). During mediastinal revision, no active hemorrhagic source was found, except for one type A aortic dissection patient undergone multiple postoperative revisions, who at the first reexploration exhibited diffuse mediastinal bleeding with a slight oozing, apparently not relevant, at the distal aortic anastomosis site.

Two patients, presented with massive ~~sero-hematic~~ sero-hemorrhagic pleural effusion requiring drainage two and four weeks after surgery. One patient experienced a right temporo-parietal intracranial hemorrhage on postoperative day 27. None of these patients were COVID-19 positive at the time of surgery. Mean blood loss from drains was markedly high (1535.25 ± 1914 [450-7465] milliliters). Mostly during the first week after surgery, nine (39%) patients experienced severe thrombocytopenia (PLTs, $<80\times10^9$ units/L), 20 (87%) patients experienced lymphocytopenia (< 10% at leukocyte formula), 7 (30%) patients exhibited prolonged prothrombin time (PT> 13 seconds). D-Dimer level, determined in 9 patients during the phase of active bleeding, was 6221.4 (357-35200) ng/mL.

The rate of surgical reexploration for bleeding in the control group, during the same enrolment period was significantly lower (2% in the control-group *vs* 35% in the study group, p = 0.0001) (Fig. 1). There was an increased need for blood component transfusion in the study group. Seventeen (74%) patients received blood products (vs 30% in the control-group, *p*= <0.01). Red cell concentrates (RCC) were used in 16 patients, PLTs concentrates in 4, and FFP in 13. Among transfused patients in the study group, the mean RCC, PLTs, and FFP administered per patient were 4.3 ± 3.7 units, 1.25 ± 0.5 units, and 1745 ± 972 mL, respectively (Fig. 1). Seventeen (74%) patients received procoagulant drugs (vs 19%, p=0.00001): 17 (74%) patients received tranexamic acid, 5 (22%) received desmopressin, and 2 (9%) received fibrinogen. In the study group sternal dehiscence was observed in 3 (13%) patients. Complications in the study group had a significant influence on length of hospital stay (17 ± 2.5 *vs* 9.2 ± 4.7 days, p=0.01). In the

multivariable logistic regression final model, SARS-CoV-2 infection and renal failure were the unique independent factors associated with postoperative bleeding complication (Table 3).

Discussion

The COVID-19 pandemic and its burden on national health systems has severely impacted services in many areas of medical care. [2-4] In addition, in many cardiothoracic surgery centers, a severe reduction of operated cases has been observed.[1,4,7-10] COVID-19 syndrome, putatively caused by coronavirus-2, is frequently characterized by acute respiratory failure with radiological signs of interstitial pneumonia, ground glass opacities and/or bilateral patchy shadowing. In some instances, ARDS and shock may also occur. [11]

A few studies investigating the clinical outcomes of COVID-19 patients ~~undergone~~ undergoing surgery, reported increased morbidity and mortality.[1,8-10] In nine COVID-19 patients undergoing cardiac surgery, Yates et al[1] reported a 44% mortality rate mainly due to severe respiratory failure. SARS-CoV-2 is a pleiotropic virus that causes several different clinical syndromes and changes in laboratory parameters, including thrombocytopenia, lymphocytopenia and a prolonged PT. [10-11]

In addition to respiratory and renal complications, COVID-19 patients may develop coagulation disorders. An increased risk for thromboembolic events has also been documented. [10-11] However little is known about the risk for perioperative bleeding complications in COVID-19 patients undergoing cardiac surgery.

In our study, we observed a marked increase in the incidence of postoperative bleeding complications compared with that noted in non-COVID-19 patients. In our Unit, during the same period, the rate of overall surgical reexplorations for bleeding in non-Covid patients undergone CPB was 4% (30 out of 750 patients) consistent with previously reported

results,[12-15] which was markedly lower than the rate of surgical reexplorations in the study-group .

Among patients with perioperative COVID-19, we observed a high rate of surgical reexploration due to bleeding, with one case of intracranial hemorrhage, two cases of massive ~~hematic~~ hemorrhagic pleural effusion, prolonged hemostasis time (i.e. SHT), conspicuous and prolonged blood loss from drains, and extensive need for blood component transfusions and procoagulant drugs.

Pathophysiological mechanisms

The pathophysiological mechanisms responsible for the observed postoperative hemorrhage in these patients are not fully understood. As reported in the literature, COVID-19 generates excessive oxidative stress caused by a “cytokine storm” characterized by hyperexpression of pro-inflammatory mediators (Interleukin-1 β, Interleukin-6 and Tumor Necrosis Factor- α) responsible for massive diffuse inflammation. [11,16-18] An overactive immune response may lead to multiple systemic effects, including direct vascular and microvascular injury with vasculitis, swelling of endothelial cells, cellular apoptosis, necrosis and a severe endothelial damage. [19-21] The angiotensin-converting enzyme II receptor (ACE-II R) expressed on the arterial and venous endothelium and arterial smooth muscle cells favors viral invasion of the vascular and microvascular tissue. This amplifies the endothelial damage with increased permeability of the capillary wall, contributing to ~~a~~ diffuse systemic bleeding, vasospasm, and, possibly, ARDS and multiple organ failure.[19-24]

(Fig. 2). A similar mechanism has been described for intracranial hemorrhagic complications occurring spontaneously or after a biopsy procedure, [25-28] and is likely to

occur with any form of bleeding during COVID-19. Furthermore, endothelial damage and diffuse bleeding could lead to thrombocytopenia, consumption of coagulation factors and fibrinolysis, with a possible clinical evolution progressing to acute Disseminated Intravascular Coagulation (DIC), thus aggravating hemorrhagic complications.[29] Moreover, ~~a~~ direct virus-mediated thrombocytopenia has been widely described.[11,30] In a multicentric analysis of 1099 patients with laboratory-confirmed COVID-19, Guan WJ et al,[11] reported a thrombocytopenia rate of 36.2%. In this vicious cycle, the inflammatory storm with endothelial damage, associated with thrombocytopenia and possible fibrinolysis may explain and justify the observed incidence of late bleeding events (Fig. 2). The observed significant increase of bleeding complications among COVID-19 patients undergoing cardiac surgery with CPB seems to support the hypotheses described.

In this study all patients underwent CPB and, in contrast to that reported in other studies,[1,5,7-10] bleeding was the most frequently encountered complication. The most likely pathophysiological mechanism is, in addition to surgical trauma, CPB-related inflammatory reaction, interstitial edema, heparinization, hemodilution, hemolysis and coagulation factor consumption, which may have contributed to precipitating postoperative hemorrhagic complications (Fig. 2). CPB could exacerbate the deleterious effect of COVID-19 on the coagulation system, leading to its disruption and a deregulation trend toward a hemorrhagic pattern. For these reasons, patients with perioperative COVID-19 undergoing cardiac surgery appear to be more susceptible to postoperative bleeding requiring mediastinal surgical revision and a high number of blood component transfusions.

We observed an increased hemorrhagic risk not only in patients with active COVID-19 at the time of surgery or early postoperatively, but also in those with healed infection before the operation, thus suggesting a possible persistent hyper-inflammatory response even after the resolution of COVID-19.

Despite the introduction of vaccines, the problem of global disease spread does not appear to be resolved. In fact, a new increase in infections has recently been observed in Europe and worldwide, and COVID-19 is still considered to be a severe comorbidity among cardiac surgery patients.[31-33] Based on our experience, it appears that the high risk for perioperative bleeding is associated not only with emergency surgery, such as aortic dissection, but also with elective surgery with no additional preoperative risk factors. Patients with perioperative COVID-19 undergoing cardiac surgery experience a poor outcome with a high rate of complications, including early and late postoperative bleeding. The aim of this study was to provide our experience promptly. We are aware that the relatively small number of patients in this initial retrospective series, the possible relative inaccuracy of certain parameters such as SHT and the lack of definitive information in the literature to support our conclusions may represent a limitation of the study. Another limitation of our study was that we included patients whose molecular diagnosis of COVID-19 was obtained in the postoperative period, and this theoretically could not have a direct influence on immediate postoperative bleeding, but rather on late hemorrhagic complications. Nevertheless, as the coronavirus incubation time remains uncertain in the literature, we selected a 7-day period to rule out postoperative SARS-COV-2 infection. Furthermore, the present study was carried out during the acute phase of COVID-19 outbreak in Italy. Therefore, here were no formal hypothesis being implemented to drive the sample size calculation and we involved the maximum number of patients who met the inclusion criteria during this critical period.

However, given that our observations appear to indicate a significantly increased risk for postoperative complications, this increased risk should be taken into consideration when assessing the operative risk ~~of~~ for patients with a perioperative diagnosis of COVID-19.

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Figure Legends

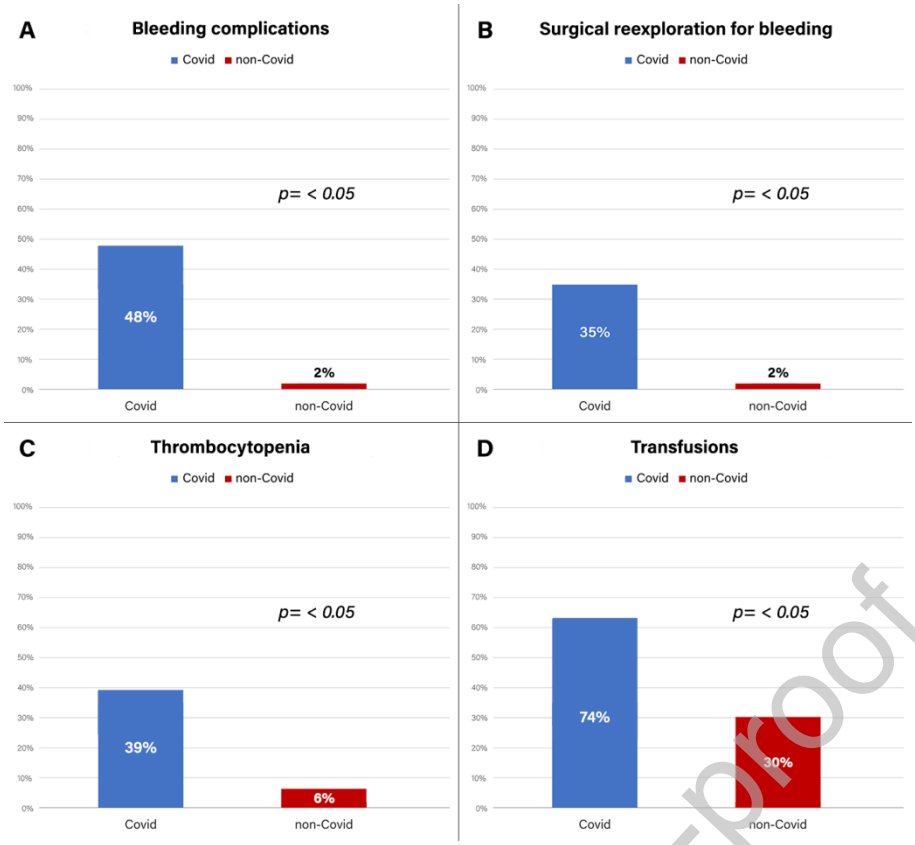

Figure 1. Incidence of bleeding complications, surgical reexploration for bleeding, severe postoperative thrombocytopenia and need of blood components transfusion in Covid and non-Covid patients.

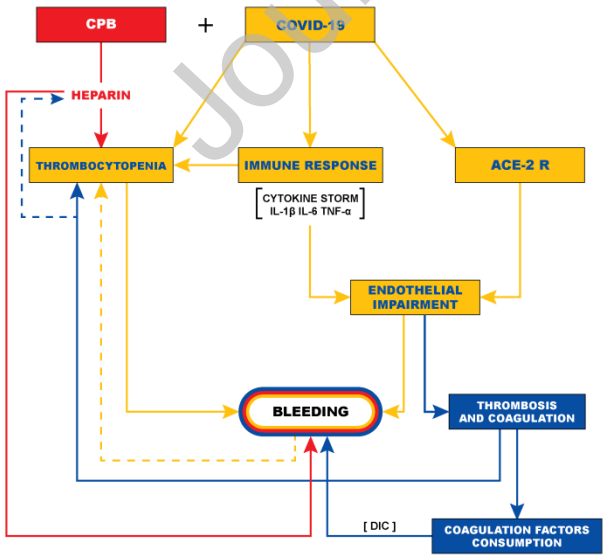

Figure 2. Possible pathophysiological mechanism of postoperative bleeding in COVID-19 patients undergoing cardiac surgery. CPB: cardiopulmonary bypass. ACE II-R: angiotensin-converting enzyme II receptor. DIC: disseminated intravascular coagulation. (References 11-30)

Table 1. Patients characteristics and operative data.

Clinical Characteristics	Covid N=23	Non Covid N=46	*p value*
Age (mean ± SD), years	68.7 ±8.3	67 ± 12.6	0.1
Female patients n (%)	4 (17)	11 (24)	0.5
BMI (mean±SD), Kg/m^2	26.6 ± 2	26.8 ± 3.4	0.1
Hypertension, n (%)	20 (87)	36 (78.2)	0.3
Diabetes, n (%)	9 (39)	7 (15)	*0.02
Dyslipidemia n(%)	11 (48)	33 (72)	0.05
Smoke habit n(%)	9 (39)	17 (37)	0.8
Renal failure, n(%)	4(17)	2 (4)	0.06
COPD n(%)	7 (30)	6 (13)	0.08
Previous NV events, n(%)	3 (13)	1 (2)	0.06
PVD, n(%)	6 (26)	4 (9)	0.05
Emergent operation n(%)	3 (13)	3 (6)	0.3
CABG isolated n(%)	7 (30)	19 (41)	-
AAR n(%)	1 (4)	2 (4)	-
AV surgery n(%)	1 (4)	6 (13)	-
MV (± TV) surgery n(%)	5 (22)	7 (15)	-
MV + AV (± TV) surgery n(%)	2 (9)	0 (0)	-
AV or MV + CABG n(%)	0 (0)	4 (9)	-
AAR + CABG n(%)	1 (4)	2 (4)	-
AAR + AV surgery n(%)	3 (13)	5 (11)	-
AVPL + AAR + CABG n(%)	2 (9)	0 (0)	-
AVPL+ AAR + ER n(%)	1(4)	1 (2)	-
Mini-sternotomy n(%)	4 (17)	9 (19)	0.8
Infective endocarditis n(%)	1 (4)	1 (2)	0.6
EF (mean ± SD) %	56 ± 7	55 ± 8	0.4
STS score-morbidity/mortality (mean±SD)%	11 ± 6.9	8.1 ± 5.8	0.3
CPB time, (mean±SD) min	152 ± 79	130 ± 45	0.08
Aortic cross clamping time (mean±SD) min	106 ± 36	86 ± 27	0.07
SHT, (mean±SD) min	81 ± 56	64 ± 45	*0.0003
ACT pre-CPB (mean±SD) sec	490 ± 87	483 ± 142	0.05
ACT post-CPB (mean±SD) sec	509 ± 140	425 ± 181	0.1

BMI: Body Mass Index (Kg/m^2); COPD: chronic obstructive pulmonary disease; NV events: neurovascular events. PVD, peripheral vascular disease; CABG, coronary artery bypass grafting; AAR, Ascending aorta replacement; AV: aortic valve; MV: mitral valve; TV: tricuspid valve; ER, emiarch replacement; EF, ejection fraction; STS score: Society of Thoracic Surgeons score; CPB, cardiopulmonary bypass; SHT, surgical hemostasis time; ACT, activated clotting time. SD: standard deviation.

*: p= < 0.05

Table 2. Postoperative results

Postoperative results	Covid N=23	Non Covid N=46	*p value*
Mortality n(%)	2 (9)	0 (0)	-
Severe respiratory failure n(%)	6 (26)	2 (4)	*0.008
Hemorrhagic complications n(%)	11 (48)	1 (2)	* 0.00001
Surgical reexploration for bleeding (patients), n(%)	8 (35)	1 (2)	*0.0001
Cardiac tamponade n(%)	4 (17)	0 (0)	-
Multiple surgical reexplorations (patients), n(%)	4 (17)	0 (0)	-
Intracranial hemorrhage n(%)	1 (4)	0 (0)	-
Pleural effusion requiring drainage, n (%)	2 (9)	0 (0)	-
Fluid loss from drains, (mean±SD) ml	1535 ± 1915	463 ±164	*0.02
Rehospitalization n(%)	2 (9)	2 (4)	0.4
Severe thrombocytopenia n (%)	9 (39)	3 (6)	*0.0007
Platelet count, *10^9/L, median (25^{th}-75^{th})	112(82-157)	176 (139-207)	*0.01
Fibrinogen, mg/dL, median (25^{th}-75^{th})	457 (331-675)	467 (362-653)	0.9
APTT, sec, median (25^{th}-75^{th})	42 (36-49)	35 (31-37)	* 0.01
Patients transfused n(%)	17 (74)	14 (30)	*0.0006
Procoagulant drugs n (%)**	17 (74)	9 (19)	*0.00001
Sternal dehiscence n (%)	3 (13)	1 (2)	0.06
Total intubation time (mean±SD) hours	13±6	10 ± 2	*0.01
Acute renal failure n (%)	2 (9)	0 (0)	-
Hemodialysis n (%)	1 (4)	0 (0)	-
Hospital stay, (mean±SD) days	17 ± 2.5	9.2 ± 4.7	* 0.01

SD: standard deviation. APTT: Activated partial thromboplastin time

*: p= < 0.05; **: tranexamic acid, desmopressin, and fibrinogen

Table 3. Logistic regression analysis of factors associated with the postoperative hemorrhagic complications.

variable	Univariate analysis		Multivariable analysis	
	OR	*p-value*	OR	*p-value*
SARS-CoV-2 infection	24	0.004	25	0.01
CPB time	1.01	0.006	---	---
Aortic cross clamping time	1	0.85		
PVD	3.25	0.14		
Renal failure	23	<0.01	24	0.01
Diabetes	0.85	0.8		

COPD	1.42	0.68		
Dyslipidemia	0.18	0.02	---	---
Platelet count, x 10^9	0.98	0.06	---	---
Fibrinogen, mg/dL	1	0.77		
Activated partial thromboplastin time, s	1.04	0.09	---	---

The following variables: dyslipidemia, CPB time, platelet count and activated partial thromboplastin time were not included in the final multivariable model.
OR: odds ratio; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CPB, cardiopulmonary bypass; PVD, peripheral vascular disease; COPD: chronic obstructive pulmonary disease.